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Glucose Metabolism in Obese Men: Abnormal Intravenous and Normal Oral Glucose Tolerance (40064)

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Obesity and its insulin resistant state are well known to pose additional risk for the development of diabetes mellitus (1). With increasing evidence that even mild degrees of hyperglycemia may hasten the development of large vessel and microvascular disease in diabetes (2) earlier detection of diabetes has been encouraged.

In the past, several studies of glucose tolerance in obese women have shown apparent preservation of intravenous glucose tolerance, but rather consistent abnormalities in the handling of orally administered glucose (3, 4). In the course of reviewing glucose tolerance in obese men, however, we have found that the opposite obtains, i.e., grossly overweight, nondiabetic men are apparently capable of preserving oral glucose tolerance while results of intravenous testing revealed abnormal disposition of the administered glucose.

Methods and materials. Eleven markedly obese male subjects (mean weight 190 ± 13% of normal; range 142–278% of ideal body weight) (5) with no personal or family history of diabetes, were studied. Mean age at time of the investigation was 38 years (range 25–49 years). All the patients were ambulatory and in good health, and received no less than 250 g of carbohydrate daily in their hospital diet for 3 days prior to testing.

After an overnight fast, and with the patient at rest, an indwelling scalp vein needle was inserted in an antecubital vein, kept open with a slow drip of heparin and saline (5 U/cc). For oral glucose tolerance testing a dose of glucose of 1 g/kg of ideal body weight and dissolved to constitute a 30% solution, was consumed within 10 min, and venous blood samples were drawn at 30, 60, 90, 120 and 180 min. For intravenous glucose tolerance testing, and with several days between the above tests, the subjects received an intravenous glucose infusion of 0.5 g/kg/ideal body weight over a 3-min period. Baseline samples were drawn, as well at 5, 15, 25, 35, 45 and 55 min after beginning the infusion of glucose.

Plasma glucose was measured by the Technicon Auto Analyzer using the method of Hoffman (6). Serum immunoreactive insulin was determined by a modification of the dextran–charcoal method (7).

The results of the oral glucose tolerance tests were evaluated using the Fajans and Conn criterion (8, 9) (glucose levels not higher than 185 mg% at 1 hr, or 140 mg% at 2 hr), the sum oral GTT/2 hrs diagnostic standard (8, 10), (summation of fasting, 1 and 2 hr plasma glucose levels), and by the Wilkerson point system (11), (fasting and 3 hr, 130 mg%; 1 point each if higher; and 1 hr 195 mg%, 2 hr 140 mg%; half point each if higher). All values are referred to measurements of glucose in plasma, which are higher than in whole blood (11).

Intravenous glucose tolerance was expressed as a function of the disappearance rate of glucose, obtained by plotting absolute glucose values semilogarithmically against time (12).

Results. Despite gross obesity each of these male subjects demonstrated oral glucose tolerance considered to be within limits by the sum of glucose levels for 2 hr (normal less than 450 mg) (8), by the Wilkerson point criteria (normal 1.5 points or less) (11) or by the Fajans and Conn criteria (normals show no more than one abnormal value at either 60 or at 120 min (8, 9) (Table I).

Despite normal oral glucose tolerance, all subjects but one displayed abnormal disappearance rates ($k < 1.20$) and in at least one third of the subjects the disappearance rates were clearly diabetic ($k = 0.9$ or less). Only one intravenous glucose tolerance was unequivocally normal ($k > 1.20$), (Table I, subject No. 11), (12).

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TABLE I

Patient No.	Weight percentile (of ideal) %	Oral glucose tolerance 2 hr SUM	60 min. (mg%)	120 min. (mg%)	Points[a] (Wilkerson)	Intravenous glucose tolerance *K* values
1	196	358	162	116	—	0.64
2	278	396	166	136	—	0.88
3	170	311	126	100	—	0.89
4	167	339	145	126	—	0.89
5	185	358	151	119	—	0.92
6	245	388	160	130	—	0.98
7	155	378	140	158	0.5	1.00
8	155	386	171	132	—	1.07
9	220	396	168	148	0.5	1.14
10	142	341	153	123	—	1.17
11	181	328	139	122	—	1.36
Mean	190	362	153	128	—	0.994
SEM	12.6	8.8	4.3	4.7	—	0.056

[a] All fasting values were below 110 mg%, and at 180 min were below 125 mg%.

No correlations were found between the summation of glucose levels for 2 hr during glucose tolerance testing (2 hr sum/GTT) (8) and the "*k*" values representing intravenous glucose disposal rate ($r = 0.0373$, p = not significant). Furthermore, no correlation could be established between the 2-hr glucose value from the oral study and disappearance rates following intravenous glucose administration ($r = 0.2108$, p = n.s.). Finally, although no significant correlation could be established between excess percentile body weight and abnormal disposition of an intravenously administered glucose load ($r = 0.231$), there was a perceptible tendency towards lower "*k*" values in the more obese patients (Table I).

When these obese men were divided into those with "*k*" values below 0.9 (clearly abnormal) and above 0.9 (borderline or normal) no significant differences were noted in either oral glucose tolerance values or serum insulin levels during both tests (Fig. 1).

However, it may be observed that the significant difference (by definition) between mean glucose values in the intravenous glucose tolerance tests, ($P < 0.025$) appear reversed, although nonsignificantly, during the oral tests. Also, higher mean insulin levels were perceptible after both the oral and intravenous glucose challenges in the group with abnormal intravenous glucose tolerance tests (Fig. 1B).

Discussion. Reports of the ability to maintain normal disposal of an intravenously administered glucose load in the face of impaired oral glucose tolerance in nondiabetic obese women (3, 4) has been associated with earlier suggestions that hepatic glycogenesis is decreased in obesity, (14) or that a rising blood sugar fails to normally dampen hepatic glucose output (3). By contrast, however, this study of oral and intravenous glucose tolerance in obese males revealed the opposite. Intravenous glucose tolerance, rather than orally administered glucose, seemed to un-

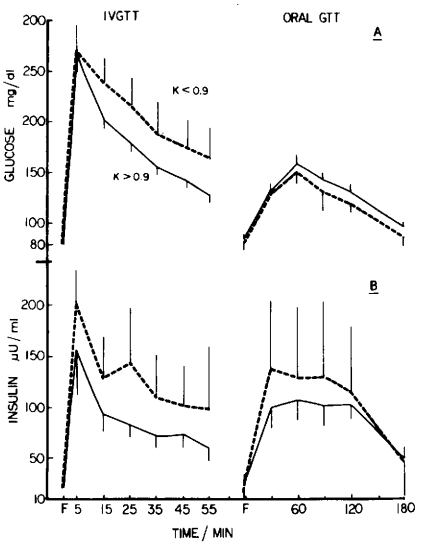

FIG. 1. A. Upper panel: Mean plasma glucose values (± SEM) during intravenous (IVGTT) and oral glucose tolerance tests (oral GTT) in obese subjects. B. Lower panel: Mean serum insulin levels (± SEM) during the same tests. Full line: patients with IVGTT disappearance rates (*K*) higher than 0.9. Interrupted line: IVGTT *K* values lower than 0.9.

mask insulin resistance although handling of the orally administered glucose load remained intact. Insulin release for those men showing impaired intravenous glucose tolerance was actually greater than for those within the group who maintained normal tolerance to both parenteral and oral routes of glucose administration. This increased insulin release was insufficient to maintain normal disposition of the intravenously administered load, but the augmented insulin release during the oral study may have more adequately insulinized the hepatocyte thereby more efficiently promoting decreased splanchnic glucose output in these subjects (14). On the other hand, the intravenous glucose tolerance test, rather than the oral test, might have evidenced peripheral resistance to glucose utilization (15), since a lower proportion of an intravenous glucose load is directly handled by the liver (16, 17).

Because these results differ so from what has been reported in overweight women, (3, 4) it may also be that there is a sex-related difference in disposal of intravenously administered glucose in obese subjects. The high incidence of impaired intravenous glucose tolerance in these obese men, reflecting greater peripheral resistance to the biologic effect of endogenously released insulin, might also suggest a difference on the basis of sex. It should be noted, however, that these obese men were probably heavier than the previously published accounts of intravenous and oral glucose tolerance testing in obese women, only defined by body weights greater than 130% (3) and 120% (4). This fact alone might account for greater peripheral insulin resistance and the results of this study.

The information from this study amplifies that caution should be exercised when attempting to accurately interpret the results of glucose tolerance testing. Both oral (18, 19) and intravenous (20) glucose tolerance tests have been shown to lack reproducibility or predictability and several reports have actually demonstrated that there can be total lack of agreement between the results of both oral and intravenous glucose tolerance testing in the same subject on different days (20–22). Other methods for investigating glucose disposal (23) have also failed to correlate exactly with the results of intravenous glucose tolerance testing, although a positive correlation with the results of glucose by mouth has been reported from studies where prolonged intravenous infusion of glucose was used (23).

Although it would be desirable to confidently quantitate the risk of becoming diabetic from the results of glucose tolerance testing, the data derived in our obese male population mostly suggest that, in the male subject, intravenous rather than oral glucose tolerance testing might reveal earlier deterioration. Whether abnormal handling of parenterally administered glucose bears any real relation to added risk for actually developing clinically significant diabetes mellitus remains to be established. Nevertheless, these results do raise the interesting possibility that there may also be a sex-related difference in hepatic glycogenesis and gluconeogenesis which bears further investigation.

Summary. Previous reports from moderately obese women have demonstrated that while intravenous glucose tolerance is generally preserved, oral glucose tolerance is frequently abnormal. On the basis of such findings it has been suggested that oral glucose tolerance testing would more reliably predict or identify the truly latent diabetic obese. In an effort to reassess this proposition, we have administered oral glucose loads and intravenous glucose challenges to 11 severely obese, otherwise healthy, male subjects. Contrary to the reports in women, intravenous glucose tolerance was abnormal or borderline in 10 of 11 men in this group, whereas oral glucose tolerance was normal by three current criteria in all subjects studied. Insulin levels rose equally high in both tests and did not correlate with these discrepant results. As a lower proportion of an intravenous glucose load is directly handled by the liver, and others have reported that hepatic resistance to the action of insulin can be reversed in the presence of high insulin levels in obesity, it is suggested that intravenous administration of glucose would unmask peripheral insulin resistance in the obese male subject.

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